## REMARKS

Upon entry of the present amendment, claims 1 and 8-15 are pending in the above-referenced patent application and are currently under examination. Claim 1 has been amended. Claims 2-7 and 16-28 have been canceled. Reconsideration of the application is respectfully requested.

Support for the amendments to claim 1 can be found in claim 1 as filed, and in the specification at page 2, line 26 to page 4, line 14. Applicants believe no new matter has been added by the amendments to the claims.

The claims are rejected in various combinations under 35 U.S.C. §§ 112, 1st, 112, 2d, 102(b) and 103(a). Each of these rejections is addressed below in the order set forth by the Examiner.

### I. REJECTION UNDER 35 U.S.C. § 112, 1st, ENABLEMENT

Claims 1-15 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse the rejection.

The test for enablement is whether the experimentation needed to practice the invention is undue or unreasonable (*Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916)) such that "the disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention" (MPEP § 2164.01).

The Examiner alleges that the specification is enabled for compounds such as 5-aza-dC and DHAdC, but does not reasonably provide enablement for any compounds encompassed by claims herein, in particular, widely varying $R^2$, $R^3$ and $R^5$-$R^{22}$ having substituted or unsubstituted alkyl, aryl, heterocycloalkyl and heteroaryl.

Applicants note that the claims have been amended in order to expedite prosecution of the Application. Specifically, claim 1 has been amended to the scope of canceled claim 5. Additional amendments to claim 1 have removed much of the language to which the

Examiner objected, i.e., "substituted or unsubstituted alkyl, aryl, heterocycloalkyl and heteroaryl." The remaining language cites specific embodiments, such as "phenyl" instead of "aryl" and "alkyloxy" instead of "heteroalkyl" (see definition of $R^{17}$). Further amendments have been made to limit $R^3$ to H and $R^8$ to unsubstituted alkyl.

As noted by the Examiner, whether undue experimentation is required to practice an invention is typically determined by the *Forman* factors. These factors weigh (i) the nature of the invention; (ii) the state of the art; (iii) the relative skill of those in the art; (iv) the predictability of the art; (v) the breadth of the claims; (vi) the amount of guidance presented; (vii) the presence of working examples; and (viii) the quantity of experimentation necessary. *Ex parte Forman*, 230 U.S.P.Q. 546 (PTO Bd. Pat. App. & Inter. 1986), *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988).

**1. The nature of the invention**

The invention is in the field of antiviral compounds, such as nucleoside and nucleotide analogues. The specific antiviral compounds of the present invention are nucleoside and nucleotide analogues. These nucleoside and nucleotide analogues are useful in the treatment of viral diseases, such as hepatitis B, hepatitis C, smallpox or HIV.

**2. The state of the prior art**

Methods of identifying nucleoside and nucleotide analogues useful for the treatment of viral diseases are known in the art. Synthetic methodologies for preparing the nucleoside and nucleotide analogues are also known in the art. Using these methods, Applicants were able to prepare and identify novel nucleotides that are useful for the treatment of viral diseases. This state of the art, when coupled with Applicants' disclosure, provides one of ordinary skill in the art with the information, moieties, and tools needed to broadly practice the invention as claimed.

**3. The relative skill of those in the art**

Applicants believe that the relative skill and experience of those in the art of nucleoside and nucleotide analogues is very high, contrary to the Examiner's assertion. Such

work is typically conducted by research enterprises populated with persons with doctorate degrees and extensive training in the relevant fields. Support for this assertion is readily evidenced by the authorship of the art disclosed with the previous IDS and discussed herein.

**4. The predictability of the art**

The field of nucleoside and nucleotide analogues is generally one in which some degree of unpredictability exists. However, the preparation of nucleoside and nucleotide analogues has exhibited a great deal of activity for many years, as evidenced by the references in the IDS, some going back to 1968. Accordingly, the Applicants submit that the field of art pertinent to the present claims is mature and very well developed.

**5. The breadth of the claims**

As noted above, the claims have been amended to address the Examiner's concerns. Specifically, claim 1 has been amended to the scope of canceled claim 5. Additional amendments to claim 1 have removed much of the language to which the Examiner objected, i.e., "substituted or unsubstituted alkyl, aryl, heterocycloalkyl and heteroaryl." The remaining language cites specific embodiments, such as "phenyl" instead of "aryl" and "alkyloxy" instead of "heteroalkyl" (see definition of $R^{17}$). Further amendments have been made to limit $R^3$ to H and $R^8$ to unsubstituted alkyl. Applicants submit that the remaining language is properly supported by the specification (see remarks below).

**6. The amount of guidance presented**

The specification provides adequate guidance for the making and using of nucleoside and nucleotide analogues of the present invention. The compounds of the present invention are made according to the Examples provided (see specifically Examples 4h and 4j), as well as according to the schemes provided in Figures 5-15 (see especially Scheme 5 in Figure 9). In addition, assays useful for testing the compounds of the present invention are taught in the specification at page 58, line 24 to page 62, line 4. Treatment methods using the compounds of the present invention are also taught in the specification at page 62, line 7 to page 66, line 2 and Examples 1-3, 5 and 6. Thus, the specification provides one of skill in the art with the necessary

teachings to make the compounds of the present invention and perform routine testing to determine the activity of the compounds. Therefore, Applicants' disclosure also sets forth all the necessary technical guidance for making the nucleoside and nucleotide analogues of the present invention.

**7. The presence of working examples**

Examples 4a-4r provides a multitude of methods for preparing nucleoside and nucleotide analogues of the present invention, such as Examples 4h and 4j. Additional teachings for the preparation of compounds of the present invention are provided by the schemes in Figures 5-15. Assays and methods of treatment using the compounds of the present invention are taught in Examples 1-3, 5 and 6. Accordingly, the specification provides sufficient examples on how to prepare the compounds of the present invention.

**8. The quantity of experimentation necessary**

The quantity of experimentation necessary[1] to practice the invention with exemplified and non-exemplified embodiments is what is routinely performed by a person of ordinary skill in the art as illustrated in the instant specification. Indeed, Examples 4a-4r provide a multitude of examples of how to prepare nucleoside and nucleotide analogues. The procedures of Examples 4a-4r can be relied upon to make compounds of the present invention, such as in Examples 4h and 4j. In addition, Examples 1-3, 5 and 6 teach routine assays for testing the compounds of the present invention and methods for using the compounds. The relative ease by which nucleoside and nucleotide analogues of the present invention can be made, greatly reduces the experimental effort required to obtain nucleoside and nucleotide analogues of the present invention.

In view of the amended claims, Applicants' respectfully submit that the specification provides the necessary teachings to enable the amended claims under 35 U.S.C. §

[1] That some experimentation may be necessary to identify operative species does not constitute a lack of enablement. As the Federal Circuit has stated, "the key word is 'undue', not 'experimentation' " in determining whether pending claims are enabled. *Wands*, 8 U.S.P.Q.2d at 1405 (Fed. Cir. 1988). Indeed, a considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance for practicing the invention.

112, 1st paragraph. Accordingly, Applicants respectfully request that the Examiner withdraw this aspect of the rejection.

## II. REJECTION UNDER 35 U.S.C. § 112, 2d

Claim 4 has been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Applicants respectfully traverse the rejection in view of the comments below.

Applicants note that claim 4 has been canceled. Accordingly, Applicants respectfully note that this aspect of the rejection is now moot.

## III. FIRST REJECTION UNDER 35 U.S.C. § 102(b) BY WIERENGA

Claim 1 has been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Wierenga (U.S. Patent No. 4,140,850). Applicants respectfully traverse the rejections in view of the comments below.

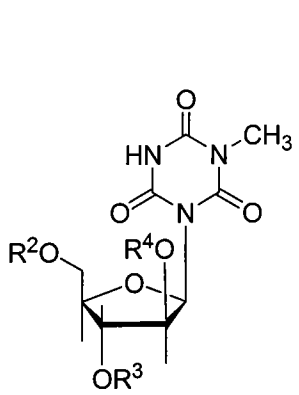
A claim is considered to be anticipated under 35 U.S.C. § 102(b) if "the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States." In order for a claim to be anticipated by a reference, the reference must teach every element of the claim (MPEP § 2131):

> A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

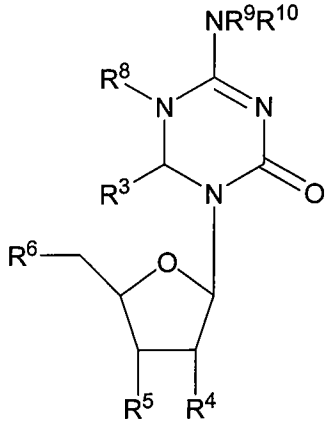
As discussed in detail below, the presently claimed invention is not anticipated in view of any of the cited references as all the references fail to teach every element set forth in the claims of the instant invention.

The Examiner alleges that Wierenga discloses the nucleoside compounds of the present invention. Applicants respectfully disagree.

The compounds of Wierenga (shown below) are characterized by a nucleoside having a 1,3,5-triazine with a carbonyl group at the 2, 4 and 6 positions, and with no unsaturation in the 1,3,5-triazine ring.




Wierenga



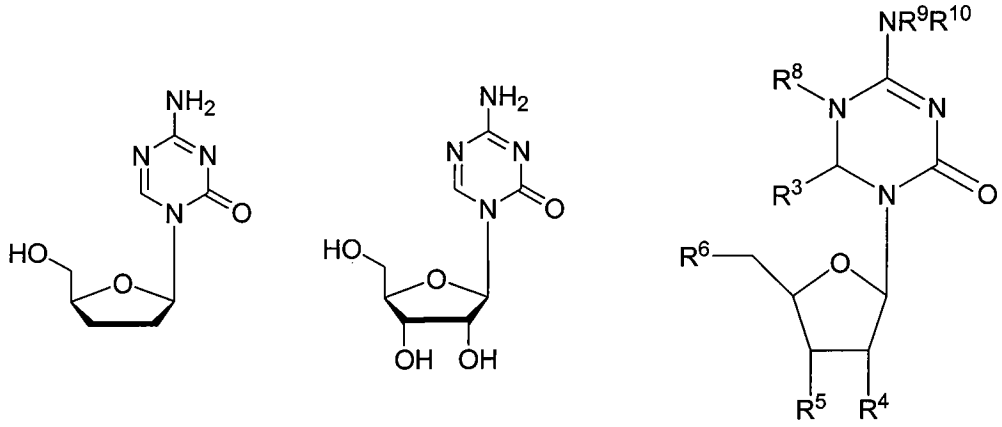

Amended claim 1

In stark contrast to the compounds of Wierenga, the nucleosides of the amended claims (shown above) are characterized by a 1,3,5-triazine with an *amine* in the 4 position and *unsaturation* in the 3,4-position. Thus, the compounds of Wierenga fail to teach all the elements of the amended claims. Accordingly, Applicants respectfully request that the Examiner withdraw this aspect of the rejection.

## IV. SECOND REJECTION UNDER 35 U.S.C. § 102(b) BY DRISCOLL *et al.*

Claim 1 has been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Driscoll *et al.* (U.S. Patent No. 4,788,181). Applicants respectfully traverse the rejections in view of the comments below.

The compounds of Driscoll (shown below) are characterized by a nucleoside having a 1,3,5-triazine with a carbonyl group at the 2 position, unsaturation at the 3,4 and 5,6 positions of the ring and no substitution at the 5-position.




Driscoll

Amended claim 1

In stark contrast to the compounds of Driscoll, the nucleosides of the amended claims (shown above) are characterized by a 1,3,5-triazine with only one point of *unsaturation* at the 3,4-position and with the 5-position being substituted with $R^8$, an unsubstituted alkyl. The 1,3,5-triazine of Driscoll cannot be substituted at the 5-position without making a quaternary nitrogen, and does not teach an unsubstituted alkyl in the 5-position of the triazine ring. Thus, the compounds of Driscoll fail to teach all the elements of the amended claims. Accordingly, Applicants respectfully request that the Examiner withdraw this aspect of the rejection.

## V. REJECTION UNDER 35 U.S.C. § 103(a) OVER DRISCOLL *et al.*, WIERENGA & MEYER

Claims 1-5 and 8-15 have been rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Driscoll *et al.* in combination with Wierenga in view of Meyer *et al.* Applicants respectfully traverse the rejection in view of the comments below.

A claim is considered obvious "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to

which said subject matter pertains" (35 U.S.C. § 103(a)). Several elements are necessary in order to make a prima facie case of obviousness (MPEP § 2143):

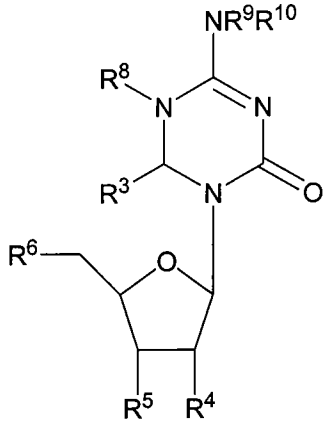
> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Accordingly, in order for the claims of the instant application to be obvious in view of the cited art, each reference must (1) provide some suggestion or motivation to modify the reference in order to teach all of the above elements; (2) provide a reasonable expectation of success of making a compound of the instant application; and (3) teach or suggest at least the above listed claim elements. As discussed in detail below, none of the cited references satisfies all three requirements under MPEP § 2143.

The Examiner alleges that provided with the references, one of skill in the art would have been motivated to select any substitution for variable R1-R18 in nucleoside compounds as taught by Driscoll and Wierenga, and combine with a second compound A-B and a polycationic carrier to form a formulation enhancing cellular uptake of the composition, as taught in Meyer. Applicants respectfully disagree.

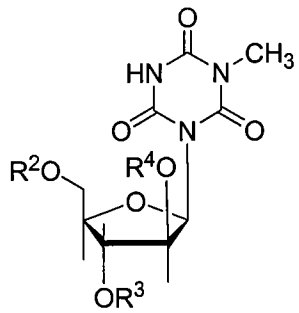
## 1. The references fail to teach or suggest all the claim limitations

Applicants note that the claims have been amended to the scope of claim 5, shown below, having an amine in the 4-position, unsaturation in the 3,4-position of the ring, and substituted in the 5-position of the triazine ring with an unsubstituted alkyl.

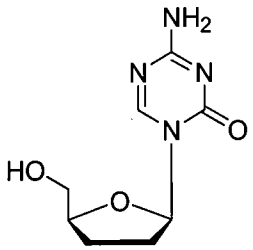


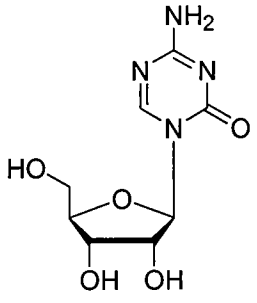

Amended claim 1

Wierenga and Driscoll *et al.*, separately and in combination, fail to teach all the elements of the amended claims. Wierenga teaches a nucleotide with a 1,3,5-triazine *without any unsaturation* in the ring, and with a *carbonyl* group in the 4-position. Driscoll *et al.* teach and disclose a nucleotide with a 1,3,5-triazine that is *fully saturated* and *unsubstituted* at the 5-position.




Wierenga




Driscoll

Applicants respectfully submit that the combination of Wierenga and Driscoll *et al.* fail to disclose or suggest all the limitations of the amended claims, as both references fail to teach or suggest an unsubstituted alkyl at the 5-position as well as 3,4-unsaturation in combination with 5,6-saturation. In addition, the teachings of Meyer *et al.* do not provide the failings of Wierenga and Driscoll *et al.* as Meyer *et al.* is drawn to peptide linkers for improving oligonucleotide delivery, and is silent as to specific oligonucleotides.

Thus, the combination of Wierenga, Driscoll *et al.* and Meyer *et al.* fail to teach or suggest all the limitations of the amended claims.

**2. There is no suggestion or motivation provided by the references or in the art itself to modify the references and arrive at the present invention.**

There is also no suggestion or motivation provided by the references or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Wierenga is drawn to 2,2'anhydrotriazine nucleosides and processes for preparing the same. The 2,2'anhydrotriazine nucleosides taught by Wierenga are fully saturated and lack *any unsaturation* in the ring, in addition to having a *carbonyl* group in the 4-position (see formula II, col. 2, lines 20-30, and compounds of Table II, col. 7, line 28 to col. 8, lines 40).

Driscoll *et al.* is drawn to 5-substituted-2',3'-dideoxycytidine compounds having anti-HTLV-III activity. The 5-substituted-2',3'-dideoxycytidine compounds taught by Driscoll *et al.* are *fully unsaturated*, and are *unsubstituted* at the 5-position (see compounds at col. 2, line 58 to col. 3, line 15 and those of Scheme 1).

Meyer *et al.* is drawn to peptide linkers for improving oligonucleotide delivery, and is silent as to specific oligonucleotides.

As Wierenga is drawn to fully saturated 2,2'-anhydrotriazine nucleosides, Driscoll *et al.* is drawn to fully unsaturated 5-substituted-2',3'-dideoxycytidine compounds and Meyer *et al.* is drawn to peptide linkers, none of the cited references provides any motivation to start with the compounds of Wierenga and Driscoll *et al.* and arrive at the 5-aza-5,6-dihydro-2-deoxycytidine compounds of the instant invention. Thus, there is no suggestion or motivation

provided by the references to combine Wierenga, Driscoll *et al.* and Meyer *et al.* and arrive at the instant invention.

### 3. There is no reasonable expectation of success provided by the references

In addition, there is no reasonable expectation of success provided by Wierenga, Driscoll *et al.* and Meyer *et al.* None of the cited references provides any motivation to combine the compounds of the references to arrive at the compounds of the present invention. Thus, there is no reasonable expectation of success provided by the references to start with the teachings of Wierenga, Driscoll *et al.* and Meyer *et al.* and arrive at the present invention.

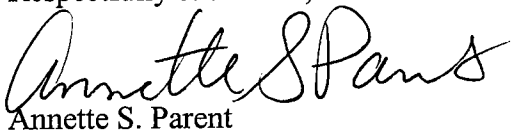
As the combination of Wierenga, Driscoll *et al.* and Meyer *et al.* fail to teach or suggest all the limitations of the instantly amended claims, and there is no suggestion or motivation to combine the references, and there is no reasonable expectation of success, the instantly amended claims are not obvious in view of the cited references. Accordingly, Applicants respectfully request that the Examiner withdraw this aspect of the rejection.

## CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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